IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC., Plaintiffs, v. EUGIA PHARMA SPECIALITIES LTD., AUROBINDO PHARMA LTD., and AUROBINDO PHARMA U.S.A., INC., Defendants.	C.A. No. 19-2309-CFC
TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC., Plaintiffs, v. ACCORD HEALTHCARE INC., Defendant.	C.A. No. 19-2321-CFC
TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC., Plaintiffs, v. MSN LABORATORIES PRIVATE LTD. and MSN PHARMACEUTICALS INC., Defendants.	C.A. No. 19-2342-CFC

TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 19-2368-CFC
NATCO PHARMA LTD. and NATCO PHARMA, INC.,	)	
Defendants.	)	

PLAINTIFFS' ANSWERING POST-TRIAL BRIEF

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TABLE OF CONTENTS

TABLE OF AUTHORITES

Page(s)

Cases

TABLE OF ABBREVIATIONS

Abbreviation	Definition
'284 patent	U.S. Patent No. RE46,284
'783 patent	U.S. Patent No. 7,799,783
'535 patent	U.S. Patent No. 6,294,535
D.I. 122	Defendants' Opening Post Trial Brief
JSUF	Joint Statement of Uncontested Facts in the Final Pretrial Order (D.I. 146-1)
FTD	trifluridine
TPI	tipiracil hydrochloride
DCR	Disease Control Rate
NDA	New Drug Application, e.g., NDA No. 207981 for LONSURF®
POSA	Person of Ordinary Skill in the Art
Hoff	Interim results from 9801 Clinical Study
Dwivedy	Interim results from 9802 Clinical Study
Thomas	Interim results from 9803 Clinical Study
Emura-II	*An Optimal Dosing Schedule for a Novel Combination Antimetabolite, TAS-102, Based on its Intracellular Metabolism and its Incorporation Into DNA* by Emura, et al.
NEJM	New England Journal of Medicine
ESMO	European Society of Medical Oncology
PPFF	Plaintiffs' Proposed Findings of Fact

I. INTRODUCTION

Plaintiffs Taiho Pharmaceutical Co. Ltd. and Taiho Oncology, Inc. ("Taiho") invented a groundbreaking cancer treatment using trifluorothymidine (FTD), a compound that prior artisans had all but abandoned for its lack of clinical utility. The industry remained skeptical until Taiho took up the mantle—Taiho, notably, is the *only* source of prior art that Defendants rely on.

The twice-daily divided dosing regimen claimed in the '284 patent is not present in the prior art—a fact not disputed by Defendants. Instead, Defendants assert that the claimed dosing regimen was obvious to try. But Defendants fail to prove such obviousness by clear and convincing evidence given that the prior art *taught away* from the claimed method. As demonstrated at trial, the prior art focused on three divided portions per day and suggested that an even larger number of divided doses was preferred in view of FTD's unique mechanism of action. Thus, persons of ordinary skill in the art would not have expected success in going the opposite direction from the teachings of the prior art. In fact, neither did Taiho when Mr. Akira Mita (an inventor of the '284 Patent) initially suggested twice daily divided dosing. Tr. 268:19-269:4 ("They couldn't believe it . . . They thought that based on the research papers and their experience up to that point in time, that three times daily or four times daily or even more frequent[] daily [dosing] would be more effective.").

The evidence presented at trial demonstrates that the dosing regimen of claim 13 of the '284 patent is a valid and nonobvious invention. Claim 13 recites a method of treating colorectal cancer orally with a combination of α,α,α-trifluorothymidine (FTD) and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride (tipiracil hydrochloride, or TPI) in a molar ratio of 1:0.5—also known as TAS-102[1] or LONSURF®. JTX-0001.0009, 9:20-34. Claim 13 is a complex dosing regimen that requires that the drug be administered "at a dose of 50 to 70 mg/m^2/day . . . ***in 2 divided portions per day***."[2] JTX-0001.0009, 9:25-26. In other words, the patient receives 2 portions per day, and the 2 portions together add up to the required 50 to 70 mg/m^2 daily dose. Claim 13 also requires that the patient receive the 2 divided portions per day "for 5 days followed by 2 days off treatment in the week on a one-week dosing schedule." JTX-0001.0009, 9:30-32.

Understanding the complexity of the dosing regimen and schedule of claim 13 is key. One component of TAS-102, FTD, is a powerful anticancer agent with

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[1] TAS-102 is the name that Taiho gave for the project that resulted in the FTD/TPI drug approved as LONSURF®.

[2] The claimed *divided* dosing regimen differs from a regimen where *multiple* doses are provided. A *divided* dosing regimen starts with a capped total amount of a drug, and divided that total into a subset of doses. A *multi-dose* regimen sets a specific amount of drug on a per dose basis (without a capped total of drug to be administered) rather than a preset total dose that is sub-divided; it then prescribes a number of times that the dose is to be administered.

demonstrated dose-limiting toxicity. Tr., 369:11-370:19 (Goldberg); DTX-333.2. FTD's anticancer activity is amplified by its incorporation into the DNA of the target tumor cells. DTX-11.1. For FTD to be effective, the tumor cells must be exposed to the drug for an extended period of time. DTX-11.1 However, each dose the patient receives must be low enough to avoid significant adverse effects. TAS-102 can therefore produce its intended anticancer effect *only if* the patient receives the appropriate total daily dose, *and* that total daily dose is divided into the appropriate number of portions, *and* that daily dose is administered on the proper schedule. Choosing whether and how to safely and effectively divide the daily dose of TAS-102 and the schedule on which it should be administered was not "simple" nor well understood at the time the application that led to the '284 patent was filed.

With that understanding of the '284 patent in mind, a proper assessment of each *Graham*[3] factor, in light of the evidence adduced at trial, shows that Defendants have failed to carry their burden of clear and convincing evidence.

Beginning with the first *Graham* factor, Defendants seemingly fail to apply the correct POSA standard by offering testimony about a hindsight-driven "hypothetical investigator." Of course the Court must apply and rely on the statutory

[3] *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

standard (POSA), who is not an "investigator," and who has none of the hindsight predilections that Defendants attempt to inject into this analysis.

Under the second *Graham* factor, the parties agree that the scope and content of the prior art does not disclose *all* limitations of claim 13. Specifically, the twice daily divided dose limitation is undisputedly not disclosed in the prior art.

Under the third *Graham* factor, Defendants have not met their burden because there are significant differences between the claimed dosing regimen and the prior art relied on by Defendants. To overcome that deficiency, Defendants levy an "obvious to try" theory by suggesting that an "investigator" would have at least tried the twice daily divided dose limitation. Defendants are wrong for multiple reasons.

First, a POSA would understand that this science—and the administration of FTD, specifically—is a deeply unpredictable area in a deeply unpredictable art. Defendants' argument to the contrary, asserting that the claimed dosing regimen and schedule is "simple," is belied by the evidence at trial. FTD had long been recognized as a potent anticancer agent, but its short half-life (about 12 minutes), prevented any practical therapeutic application of FTD alone. DTX-11.1; Tr., 369:11-370:19 (Goldberg). Taiho attempted to address this shortcoming by combining FTD with TPI, a thymidine phosphorylase inhibitor, which slows the degradation of FTD and allows it to have a greater therapeutic effect. JTX-0001.0005, 2:16-21; Tr., 348:13-18 (Goldberg). The resulting combination (TAS-

102), was promising but still resulted in adverse events in humans when administered in various once-daily (i.e., undivided) dosing schedules. PTX-0534 (Hoff); PTX-0533 (Dwivedy); PTX-538 (Thomas); JTX-0012.0860. It was not until the development of the complex twice daily divided dosing regimen of claim 13—with the specific dose, molar ratio, dosing schedule and frequency of divided dosing—that FTD finally achieved the desired therapeutic result without severe adverse events.

Second, given FTD's short half-life, the prior art affirmatively taught away from a two-dose divided regimen. Unlike traditional cancer treatments, which rely on overwhelming concentration in a dose to destroy cancer cells, FTD operates differently. The critical basis for the efficacy of FTD was the amount of time that it was in physical contact with cancer cells. That is because rather than brute force destruction of the cancer cells, which typifies traditional cancer treatments, FTD's operative mechanism is that it *binds with the DNA* of cancer cells and causes follow-on cancer cells to self-destruct. FTD needs time for that binding to occur—and the prior art taught, the more time, the better. As a result, the prior art taught a *higher* number of doses (3+) in order to achieve effectiveness. *See supra* Section III.C.1.

The patented method, however, went the opposite direction. Rather than taking three or more divided doses, the '284 patent taught that FTD ought to be in contact with cancer cells for *less* time—a twice-divided dose. Despite being in

contact with the cancer cells for *less* time, the '284 patent revealed that a twice-divided dose was, contrary to expectations, *more* effective at treating cancer. The '284 patent's approach was 180-degrees in the opposite direction from the prior art. This is not merely Taiho's view. The Patent Office was presented with the same clinical data on a reexamination of the underlying patent and determined that twice-divided dosing had "unexpected" success relative to prior art teachings, explicitly articulating that point in the Notice of Allowance for the '284 patent.

Third, Defendants do not persuasively explain why a POSA would have adapted Dwivedy's schedule with Emura's dosing regimen, given (1) Dwivedy's disparagement of its own results (unsuccessful) and its own schedule, and (2) the availability of superior follow-on studies that applied different schedules with greater success. As of the filing date of the '284 patent, a POSA would have known that Thomas (the third trial) was developed as an improvement to Hoff (the first) and Dwivedy (the second), and Thomas demonstrated a higher maximum tolerable daily, undivided dose and provided the most convenient schedule. Thus, if a POSA would have been motivated to make additional modifications to the known dosing methods of TAS-102, a POSA would have been discouraged from starting with Dwivedy and would have been motivated to start with Thomas.

Finally, the fourth *Graham* factor exclusively counsels against a finding of non-obviousness. The unrebutted evidence shows that twice-daily divided dosing

delivered unexpectedly, superior results to what was expected by the prior art. Moreover, by overcoming the failures of the prior art regimens, the inventors of the '284 patent fulfilled a long-felt need for a treatment for Stage IV colorectal cancer treatment that meaningfully extends patients' lives while maintaining their quality of life. These benefits have been recognized throughout the industry and led directly to significant commercial success for LONSURF®. Defendants largely do not dispute these facts; instead, they dispute the nexus requirement. But Defendants' nexus argument is foreclosed by *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1378 (Fed. Cir. 2021), and Defendants fail to refute the evidence Taiho adduced tying LONSURF® to claim 13 of the '284 patent.

Finally, Defendants' half-hearted written description defense falls flat. In less than three pages, Defendants argue that the '284 patent does not adequately describe the claimed dosing regimen. However, Defendants ignore the fact the '284 patent expressly describes twice-daily divided dosing and treatment of colorectal cancer.

II. PROSECUTION HISTORY OF THE '284 PATENT

A. Taiho Files A Reissue Application to Put All of the Relevant Prior Art Before the USPTO

After the '783 patent issued, Taiho discovered that an article authored by Inventor Emura ("Emura-II," DTX-11), was published on January 19, 2004—earlier than originally believed, and one week before the January 26, 2004 critical date—and was therefore prior art to the '783 patent. Emura-II found that dosing mice in

three divided portions per day "resulted in enhancement of the antitumor effects of TAS-102 without any additional side effects." DTX-11.1. Having discovered that Emura-II was in fact prior art, on December 30, 2015, Taiho filed a reissue application for the '783 patent. *See* JTX-0012.0001, 0004.

Along with Emura-II, Taiho put several other prior art references before the USPTO, including abstracts summarizing the three phase I studies conducted on TAS-102: Hoff, Dwivedy, and Thomas.[4] JTX-0012.0076-82 (Emura-II) (Ex. F); 0103 (Hoff) (Ex. K); 0116 (Dwivedy) (Ex. L); 0134 (Thomas) (Ex. M). Each abstract disclosed a different dosing regimen and schedule for TAS-102, all with a once-daily (i.e., undivided) dose:

Publication Date	**Abstract**	**Dosing Regimen**	**Dose ($mg/m^2/day$)**	**Dosing Schedule**
November 2000	Hoff (9801)	Once daily (undivided)	50-100	14 days every 21 days
May 2001	Dwivedy (9802)	Once daily (undivided)	50, 70, 80	5 days a week for 2 weeks, repeated every 4 weeks
March 2002	Thomas (9803)	Once daily (undivided)	100, 110, 120, 130, 140	5 days every 21 days

PTX-0534; PTX-0533; PTX-0538.

[4] Taiho referred to the phase I trial interim results discussed by Hoff (PTX-0534) as "the 9801 study," Dwivedy (PTX-0533) as "the 9802 study," and Thomas (PTX-0538) as "the 9803 study." Tr., 430:15-18 (Goldberg).

B. Taiho Demonstrates that Twice-Daily Divided Dosing Was Unexpectedly Superior to Three-Times-Daily Divided Dosing

In support of the patentability of the amended claims, Taiho submitted the declaration of Mr. Mita, which showed that the claimed twice daily divided dosing regimen had unexpectedly superior efficacy and safety results compared to the three-times daily divided dosing taught by Emura-II. *See* JTX-0012.0859-68. The surprising and unexpected nature of the claimed twice daily divided dosing regimen is discussed in Section III.D.1, *infra*. The Examiner understood the significance of these surprising and unexpected results, noting in the Notice of Allowance that: (1) "the dosing schedules claimed are below the effective minimum dose taught by Emura *et al.* which suggested three times daily dosing of the FTD/TPI combination would be the best protocol for treatment in humans;" (2) "[t]his claimed twice-daily dosing protocol shows efficacy in human clinical trials, but also shows reduced adverse patient events;" and (3) "[i]t was unexpectedly found that more tumors shrunk when treated with the twice-daily dosing schedule than with the three-dose daily dosing schedule." JTX-0012.1333. The USPTO then issued the '284 patent.

III. DEFENDANTS FAILED TO PROVE BY CLEAR AND CONVINCING EVIDENCE THAT CLAIM 13 OF THE '284 PATENT WOULD HAVE BEEN OBVIOUS

Defendants have failed to establish by clear and convincing evidence that "the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the

claimed invention to a person having ordinary skill in the art." 35 U.S.C. §103 (pre-AIA). Obviousness is a question of law predicated on factual determinations, including: (1) the level of ordinary skill; (2) the scope and content of the prior art; (3) the differences between the claimed subject matter and the prior art; and (4) objective indicia of non-obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

"The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008); 35 U.S.C. § 103. This is because "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418-19 (2007). An "invention is not obvious simply because all of the claimed limitations were known in the prior art at the time of the invention." *Forest Labs., LLC v. Sigmapharm Labs., LLC*, 918 F.3d 928, 934 (Fed. Cir. 2019); *accord KSR*, 550 U.S. at 420.

Defendants had the burden not only to prove that each limitation of claim 13 is found in the prior art, but also to "prove 'by clear and convincing evidence that a skilled artisan would have been ***motivated to combine*** the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a ***reasonable expectation of success*** in doing so.'" *Novartis Pharms. Corp. v.*

West-Ward Pharms. Int'l Ltd., 923 F.3d 1051, 1059 (Fed. Cir. 2019) (emphasis added). "The presence or absence of a motivation to combine" and the "presence or absence of a reasonable expectation of success" are questions of fact. *Id.* (quoting *Par Pharm., Inc. v. TWI Pharms., Inc*., 773 F.3d 1186, 1196 (Fed. Cir. 2014)). Defendants failed to prove these facts at trial.

Finally, "[t]he U.S. Federal Circuit Court of Appeals has consistently admonished that 'an examiner's decision on an original or reissue application is evidence the court *must* consider in determining whether the party asserting invalidity has met its statutory burden by clear and convincing evidence, and that, upon reissue, the burden of proving invalidity was made heavier.'" *Broussard v. Go-Devil Mfg. Co.*, No. 3:08-CV-00124-BAJ, 2014 WL 46632, at *3 (M.D. La. Jan. 6, 2014) (quoting *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 961 (Fed. Cir. 1986).

A. Person of Ordinary Skill in the Art

The parties agreed that a POSA, as of January 2005, would be a physician with a medical degree and at least five years of practical experience in the clinical treatment of cancer patients. The POSA would have at least 2-3 years of residency or fellowship training in oncology and would be an oncologist in the everyday practice of treating cancer patients. JSUF, ¶36. Because the drug development process is multidisciplinary, the person would have at least practical training in one

or more areas of pharmacy, pharmaceutical sciences, preclinical and clinical drug development, medicine, pharmacokinetics and/or pharmacology. JSUF, ¶37.

The POSA in this case is a practicing physician; not an "investigator" (hypothetical or otherwise) as Defendants repeated throughout trial and in its post-trial brief. By using the term "hypothetical investigator," Defendants improperly suggest that the Court's inquiry should be placed on persons focusing on clinical trials who are "adjusting only the doses per day" (Tr. at 21:8-23), but that is quintessential hindsight. *See, Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) ("Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.") (internal citation omitted). The POSA in this case would have read and understood all the teachings of the prior art—including the teachings away discussed below. "The determination of the level of ordinary skill in the art is an integral part of the *Graham* analysis." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 666 (Fed. Cir. 2000). Defendants' failure to use the correct POSA standard does not aid the Court in its ultimate determination of this matter.

B. Scope and Content of the Prior Art

Defendants rely only on three prior art references to assert obviousness: (1) Dwivedy (DTX-8/PTX-0533); (2) Emura-II (DTX-11); and (3) the '535 patent (DTX-362) (collectively, the "Relied on Prior Art"). All three references were

before the USPTO during reissue examination of the '284 patent.[5] PPFF 17, 37. As the chart below reflects, the Relied on Prior Art does not teach every limitation of claim 13. PPFF 44, 50, 55, 59-61, 63.

Claim 13 & Relied on Prior Art	Compounds	Molar Ratio	Max. dose/day based on antitumor agent	Dosing Regimen	Dosing Schedule
Claim 13 of '284 Patent	**FTD + TPI**	**1:0.5**	**50-70 mg/m^2**	**2 Divided Portions per Day**	**5 days on / 2 days off in a week**
'535 Patent (DTX-362)	Hundreds of uracil compounds and fluoropyrimidine antitumor agents containing 2'-deoxypyrimdine nucleosides	Wide range of ratios disclosed, with specific ratios tested from 1:0.2 - 1:5	Huge ranges for both compounds.	Both Undivided and Divided	No schedule disclosed
Dwivedy Abstract (DTX-8/PTX-0533)	TAS-102 (FTD + TPI)	Not disclosed	80 mg/m^2	Undivided	5 days on / 2 days off
Emura-II (DTX-11)	TAS-102 (FTD + TPI)	1:0.5	150 mg/kg (mice)	Undivided & three-times daily divided	1 or 3 days (mice)

[5] "[A] party challenging validity shoulders an enhanced burden if the invalidity arguments relies on the same prior art considered during examination by the [PTO]." *Tokai Corp. v. Easton Enters.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011); *see also Tris Pharma, Inc. v. Actavis Labs. FL, Inc.*, 503 F. Supp. 3d 183, 203 (D. Del. 2020).

C. There Are Significant Differences Between Claim 13 and the Prior Art

1. The Relied on Prior Art Does Not Disclose All of the Elements of Claim 13

Claim 13 recites a method of treating colorectal cancer orally with a combination of α,α,α-trifluorothymidine (FTD) and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride (tipiracil hydrochloride, or TPI) in a molar ratio of 1:0.5—also known as TAS-102 or LONSURF®. JTX-0001.0009, 9:20-34. One component of TAS-102, FTD, is a powerful anticancer agent with demonstrated dose-limiting toxicity. Tr., 369:11-370:19 (Goldberg); DTX-333.2. Unlike other 2'-deoxypyrimidine nucleosides, FTD's anticancer activity is amplified by its incorporation into the DNA of the target tumor cells. DTX-11.1. For FTD to be incorporated effectively, the tumor cells must be exposed to the drug for an extended period of time. DTX-11.1. However, each dose the patient receives must be low enough to avoid significant adverse effects. TAS-102 can therefore produce its intended anticancer effect *only if* the patient receives the appropriate total daily dose, *and* that total daily dose is divided into the appropriate number of portions, *and* that daily dose is administered on the proper schedule.

Claim 13 also recites a complex dosing regimen that requires that the drug be administered "at a dose of 50 to 70 mg/m^2/day . . . ***in 2 divided portions per day***." JTX-0001.0009, 9:25-26. In other words, the patient receives 2 portions per day,

and the 2 portions together add up to the required 50 to 70 mg/m^2 daily dose. Adding further complexity, claim 13 requires that the patient receive the required dose in 2 divided portions per day "for 5 days followed by 2 days off treatment in the week on a one-week dosing schedule." JTX-0001.0009, 9:30-32. FTD has long been recognized as a potent anticancer agent, but its short half-life, about 12 minutes, historically prevented any practical therapeutic application of FTD alone. DTX-11.1. Taiho addressed FTD's short half-life by combining it with TPI, a thymidine phosphorylase inhibitor, which slows the degradation of FTD and allows it to have a therapeutic effect. JTX-0001.0005, 2:16-21. The resulting combination, TAS-102, was promising but still resulted in adverse events in humans when administered on various once-daily (i.e., undivided) dosing schedules. PTX-0534 (Hoff); PTX-0533 (Dwivedy); PTX-0538 (Thomas). It was not until the development of the complex twice daily divided dosing regimen of claim 13— with the specific dose, molar ratio, dosing schedule and frequency of divided dosing—that FTD could be administered to patients in a manner that achieved the desired therapeutic result.

It is undisputed that the Relied on Prior Art does not disclose every element of claim 13. Among other things, Defendants admit that twice-daily divided dosing is not taught in the prior art. Tr., 527:23-24. Neither the Dwivedy abstract nor the '535 patent identifies the exact combination of compounds (FTD and TPI) set forth in claim 13, which is significant given FTD's unique mechanism of action. DTX-

11.1 (describing action of incorporating into DNA). Only Emura-II discloses the use of FTD with TPI; only Emura-II recognizes FTD's unique mechanism of action; and only Emura-II explains—after conducting experiments in mice—that there remains the unsolved problem of identifying a means for administering the drug combination in a manner that would permit the "efficient incorporation of [FTD] into DNA . . . for maximally exerting the antitumor activity of FTD." DTX-11.6. But nothing in Emura-II suggests that dosing in only ***two*** divided portions per day would result in appropriate levels of FTD exposure or reduce potential adverse events; rather, the prior art taught away from any such understanding.

2. The Full Scope of Prior Art Teaches Away From the Limitations of Claim 13

Obviousness "cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013). "Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011) (internal quotations omitted). Rather, when examining the prior art, there must be a reason to select the known elements as starting points. *KSR*, 550 U.S. at 418-21. Additionally, references must be considered "as a whole, including portions that would lead away from the

invention in suit." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987).

Rather than consider the full scope of prior art available to a POSA, Defendants employ improper hindsight bias in focusing only on the prior art that most closely resembled claim 13, while ignoring other teachings from the prior art that taught away from the claimed invention. For example, Defendants focus on Dwivedy, the second of three Phase I studies testing various dosing amounts and schedules of TAS-102, but essentially ignore the other two Phase I clinical studies—even though the Dwivedy regimen proved less effective. As discussed below, Dwivedy's relative ineffectiveness means a POSA would have understood it as less effective than the other studies, and therefore would not have relied on it.

Defendants fail to justify their mosaic-like approach to assembling the claims from disparate portions of the prior art. Defendants also selectively pick and choose from a number of dosing schedules used in clinical trials of other chemotherapy drugs (e.g., UFT and S-1), to create the misimpression that such drugs were only being tested with dosing schedules similar to that of the claimed invention. D.I. 122 at 14, 18-19, 28, 32. This incomplete characterization of the prior art is of little relevance. FTD, even when combined with TPI (TAS-102), has a different mechanism of action than other chemotherapeutic agents, and thus faces different

development challenges. Defendants do not make the necessary showing that a POSA would have treated different drugs as instructive.

For example, while Dr. Ratain explained that UFT had been tested with a 5 day on, 2 day off schedule (Tr., 113:10-114:8), there were at least seven other UFT studies in the same timeframe testing a variety of dosing schedules, including fourteen days every three weeks, (as in Hoff), twenty-one days every four weeks, fourteen days every four weeks, among other schedules. DTX-235.16. At the same time, UFT was undergoing clinical tests at once, twice, and three-times daily dosing. DTX-235.16, 17, 19. In addition, while DTX-247, which was shown to Dr. Goldberg on cross examination, shows a 5 day on, 2 day off schedule tested for a combination of UFT and leucovorin, it was actually administered three-times daily in that study. DTX-247.2. Another drug Defendants reference, S-1, was being studied with both once and twice-daily dosing. *See* DTX-235.24.

Defendants' selective, hindsight-based reliance on only some portions of these contemporary studies, while ignoring other portions that teach away from the claimed invention should be given no weight in the obviousness determination.

3. Combining the Prior Art Together Does Not Disclose All of the Limitations in Claim 13

"[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention." *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064,

1073 (Fed. Cir. 2015) (emphasis added). There cannot be obviousness when the prior art provided no "reason to select (among several unpredictable alternatives) the exact route" to the invention." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). Even if the POSA in this case had chosen the most advantageous compounds, molar ratio, dosing regimen, and dosing schedule known in the art, the POSA still would not have arrived at the limitations of claim 13. Defendants are thus relegated to arguing that the method of claim 13 was "obvious to try," a theory that they cannot establish in this case.

4. The Patented Method of Claim 13 Was Not "Obvious to Try"

i. "Obvious to Try" Requires a Finite Number of Predictable Solutions; Not General Experimentation

As the Supreme Court stated in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), an invention may be obvious to try "[w]hen there is a design need or market pressure to solve a problem *and there are a finite number of identified, predictable solutions*." *Id*. at 421 (emphasis added). Both before and after *KSR*, the Federal Circuit has consistently held that "obvious to try" does not render obvious a patented invention where the properties of that invention or the methods of obtaining it were not predictable, or where there was no reasonable expectation of success. This is especially so where a skilled artisan must "explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art

gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

Here, the trial record shows that the prior art provided a number of different approaches to administering TAS-102 in a multitude of different dosages, using different dosing regimens and applying different dosing schedules—none of which, however, were considered successful by January 26, 2005. "The Court in *KSR* did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008). "[A] conclusion of obviousness does not follow from merely vary[ing] all parameters or try[ing] each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Grunenthal GmbH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1345 (Fed Cir. 2019) (internal quotation marks omitted). Defendants cannot satisfy this burden because the prior art and the evidence adduced at trial pointed in the *opposite direction* of the claimed invention.

ii. The Prior Art Taught Away from Using Two Divided Portions Per Day of FTD

Defendants did not demonstrate by clear and convincing evidence that a POSA would have been motivated to choose an unproven, unsupported treatment

regimen (twice-daily divided dosing) that had never been tested in animals or humans. The information available to a POSA at the time of the invention about (i) *the half-life of FTD* (12 mins); (ii) *the mechanism of action of FTD* (incorporation into DNA in a time dependent manner); and (iii) *the toxicity of FTD* (adverse events) all taught away from the claimed invention and would have directed a POSA towards *three or more divided doses per day*—two divided doses was in the opposite direction and contrary to the teachings of the prior art.

FTD has a very short half-life of about 12 minutes. Tr., 144:4 (Ratain); Tr., 348:13-15 (Goldberg). The half-life of FTD had been understood since at least 1970. JTX-0012.0088, 0090; JTX-0001.0005, 2:1-7. Understanding this short half-life, Ansfield administered FTD alone every three hours for a total of *eight daily doses*. DTX-333.2. But FTD, even when combined with TPI to form TAS-102, still resulted in adverse events in humans when administered on a once-daily (i.e., undivided) dosing schedule. PTX-0533 (Dwivedy).

With this background in mind, Emura-II hypothesized that if TAS-102 were administered in a three-times daily ***divided*** dose at 3-hour intervals, the FTD could contact tumor cells "at a several-micro molar range" for an extended period of time sufficient to enhance the drug's anticancer effect. DTX-11.4-5. Indeed, when Emura-II compared groups of mice receiving once-daily ***undivided*** doses of TAS-102 (100 mg/kg or 150 mg/kg single daily dose) to groups of mice receiving three-

times daily ***divided*** doses of TAS 102 (90 mg/kg/day divided into three 30mg/kg doses, or 150 mg/kg/day divided into three 50 mg/kg doses), they found that "FTD incorporation into DNA was enhanced by [the three-times daily] ***divided*** dosing modality." DTX-11.3, 5.

Among the treatment groups, Emura-II found that the mice receiving 150 mg/kg/day divided into three 50 mg/kg doses had a "significantly enhanced [] antitumor effect" and stated that "incorporation of FTD into DNA may be increased by [three-times divided daily dosing] of 50 mg/kg each compared to single [undivided] dosing of 150 mg/kg." DTX-11.6. As Dr. Goldberg explained, Emura-II suggests that "exposure to significant drug levels over ten hours would be ideal," making it optimal to administer three doses three hours apart. Tr., 348:10-21 (Goldberg). Emura-II concluded that "[t]he present protocol [(3 dose portions daily)] seems well advised." DTX-11.6. Moving from a ***single, undivided dose*** to ***a three-times daily divided dose*** offered improved efficacy by extending the length of time tumor cells were exposed to the drug (even in view of its short half-life).

Moving to a three-times daily divided dose also offered a chance to further decrease adverse events by avoiding a single large dose of FTD, which was known to have significant adverse effects. As a POSA would have understood, when a dose is divided into more than one portion per day (i.e., two, three or even more portions), the amount of drug in each portion decreases as the number of portions increases.

The benefits of three-times daily dosing that Emura-II demonstrated (DTX-11.2, 5-6), in the context of the other art available at the time, would have taught a POSA to continue moving toward three or more (smaller, more frequent) divided dose portions per day, rather than to move backward to two (larger, less frequent) divided dose portions per day. *See KSR*, 550 U.S. at 416 ("The Court relied upon the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious") (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)).

Dr. Goldberg explained that it would *not* have been expected that twice-daily dosing of a "drug combination that has a 1.4-hour half-life would be better than three-times-a-day dosing where longer exposure could have potentially led to longer – or to greater incorporation of the drug into DNA." Tr., 450:20-25; *see also* DTX-11; DTX-333.

Dr. Ratain did not contradict Dr. Goldberg. Instead, Dr. Ratain testified that "dividing the dose, [] into two or three portions would certainly be ***feasible***." Tr., 164:24-165:4 (emphasis added). Feasibility is a far cry from an explaining whether a POSA would have a reasonable expectation of success. *See ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (rejecting conclusory expert testimony focused merely on the fact that a POSA would have known how to combine the various elements to arrive at the claimed invention). This

testimony from Defendants' expert falls well short of demonstrating by clear and convincing evidence that the POSA would have had a reasonable expectation of success in modifying the prior art to arrive at the claimed invention, especially the twice-daily-divided dosing element. Given these teachings, a POSA would not have been motivated to decrease the number of dose portions to two. Instead, the POSA would have been motivated to increase the number of divided doses to three or more.

iii. The Prior Art Taught Away from Using a Dosing Schedule of 5-days On and 2-days Off

When considering whether a particular dosing schedule was obvious to try, a POSA must take into consideration the actions of the people performing these clinical trials. Here, there is a clear record of the iterative process involving TAS-102, and Defendants have provided no evidence or reasoning to contradict that work.

The evidence shows that the TAS-102 researchers started their work with the Hoff study. PTX-0534. Based on Hoff, researchers then performed the Dwivedy study. PTX-0533. Based on Dwivedy, researchers then performed the Thomas study. PTX-0538. Notably, despite doing three separate studies, the researchers never divided the daily doses. Instead, they kept the undivided dosing regimen and focused on modifying the dosing schedule.

As of January 26, 2005, a POSA would have known that Thomas, which was developed based on all information available from Hoff and Dwivedy, demonstrated a higher maximum tolerable daily, undivided dose and provided the most convenient

schedule. Tr., 345:17-18. Thus, if a POSA would have been motivated to make additional modifications to the known dosing methods of TAS-102, the POSA would have started with Thomas.

Yet Dr. Ratain and Defendants willfully ignore the dosing schedule taught by Thomas. The first study, Hoff, administered TAS-102 in doses ranging from 50-100 mg/m^2/day for 14 days every 21 days (2 weeks on, 1 week off). PTX-0534. Dwivedy was the second study. PTX-0533. The third, Thomas, administered TAS-102 in doses ranging from 100-140 mg/m^2/day for 5 days every 21 days. PTX-0538. Of these three Phase I trials, Dwivedy reported the lowest disease control rate ("DCR").[6] Dwivedy reported results in 12 patients, with only one exhibiting stable disease (DCR = 8%). PTX-0533; JTX-0012.0128. In contrast, Hoff reported results for 14 patients, with 5 patients exhibiting stable disease (DCR = 36%). PTX-0534. Thomas reported results for 21 patients, with 4 patients exhibiting stable disease (DCR = 19%). PTX-0538; JTX-0012.0145. Given all the available information, the TAS-102 researchers chose to move away from the Dwivedy schedule to the Thomas schedule. This could be due, in part, to the fact that Dwivedy produced a low DCR.

[6] DCR is an indication of a drug's efficacy. JTX-0012.1280 (Exhibit Q identifies DCR as a category considered for efficacy. DCR "shows the percentage of patients who exhibited reduction of tumor size or inhibition of tumor growth for a certain period," with evaluation using the RECIST criteria); *see also* JTX-0023.0003, 0006 (NEJM article addressing DCR as a secondary endpoint of efficacy).

Given the Thomas results, a POSA would not have retreated back to the dosing schedule that produced the lowest DCR.

Defendants offer no plausible explanation for why a POSA would have chosen the dosing schedule of Dwivedy over Hoff or Thomas. Dr. Ratain never explained why a POSA would have chosen the older, less effective, more complicated Dwivedy dosing schedule. Such conclusory testimony is insufficient for Defendants to carry their burden. *See Upjohn Co. v. Mova Pharm. Corp.*, 225 F.3d 1306, 1311 (Fed. Cir. 2000) ("At this critical point in the determination of obviousness, there must be factual support for an expert's conclusory opinion"). Put simply, the evidence does not demonstrate a clear reason to start with the Dwivedy schedule. *See KSR*, 550 U.S. at 418-21. The only explanation for Defendants' selection of Dwivedy is that it is based on improper hindsight.

Indeed, Dr. Goldberg confirmed that the Thomas dosing schedule would be the easiest to prescribe: "In my mind, five days out of every three weeks would be easiest." Tr., 345:17-18. Dr. Goldberg's second choice would be Hoff: "Two weeks out of every three weeks would be next easiest." Tr., 345:18-19. He also explained that the dosing schedule in Dwivedy is "a more complicated regimen and not one that U.S. patients had commonly been prescribed in the past." Tr., 345:23-25. Defendants and their expert agree on this point. *See* D.I. 122 at 45 (referring to Hofmann testimony and contending that the "complicated" dosing schedule of claim

13 had a "negative impact" on marketplace performance). And contrary to Defendants' suggestion, Dr. Goldberg's testimony that Dwivedy presented the most complicated schedule is not based on hindsight. Dr. Goldberg did not base his testimony solely on his experience actually prescribing Lonsurf. Dr. Goldberg was a physician in 2005 and his testimony was based on his review of the schedules disclosed in the art. Tr., 345:13-25.[7]

D. Objective Evidence Supports the Non-obviousness of Claim 13 of the '284 Patent

The objective evidence presented by Taiho confirms the non-obviousness of claim 13. These real-world facts are "crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013); *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). Indeed, objective indicia "may often be the most probative and cogent evidence of nonobviousness in the record." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). Taiho bears a "burden of production" in showing the existence of objective indicia by a

[7] At trial, Dr. Goldberg was asked whether a POSA would have been motivated to combine Dwivedy with Emura-II. In response, Dr. Goldberg explained "the iterative process of developing new drugs requires using *all the data that is possibly available* . . . includ[ing] the three clinical study reports [*i.e.*, Hoff, Thomas and Dwivedy]." Defendants, however, mischaracterize the foregoing testimony to suggest, erroneously, that Dr. Goldberg admitted that a POSA would have simply combined Dwivedy and Emura-II. D.I. 122 at 26, 29-30.

preponderance of the evidence. *Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1101-02 (Fed. Cir. 2015). However, the burden of proving invalidity remains with Defendants.

In this case, unexpected results, long-felt but unmet need, industry praise, and commercial success provide strong objective evidence that the claimed invention is non-obvious.

1. The Claimed Dosing Regimen Led to Unexpected Results

Unexpected results are evidence of non-obviousness because "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). This factor is particularly relevant in "the less predictable fields," such as cancer treatments, "where minor changes in a product or process may yield substantially different results." *Id.*; *see also Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d 377, 400 (D. Del. 2021), *aff'd sub nom. Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006 (Fed. Cir. Nov. 15, 2022) ("Cancer treatment can be unpredictable.").

As discussed above, Emura-II demonstrated that dividing the daily dose into three or more parts was more effective than giving the same total dose in an undivided single administration. With these data in mind, Taiho decided to perform Phase I clinical studies using a three-times-daily divided dosing regimen. However,

Mr. Mita also suggested gathering data on a ***twice***-daily divided dose. JTX-0012.0860, ¶3.

Mr. Mita's suggestion ran counter to everything a POSA would have understood about dosing TAS-102 at the time the '284 patent was filed. Emura-II (DTX-11.6) had demonstrated that compared to a single daily dose, dividing the total daily dose into ***three*** smaller, more frequent portions resulted in improved efficacy. JTX-012.0860, ¶3. Takeda (PTX-0523.0002-03) demonstrated that FTD alone was more effective when the daily dose was divided into four portions. JTX-0012.0860, ¶3. Yet ***Mr. Mita proposed moving backward***—dividing the total daily dose into just two portions (necessarily making each portion larger than it would have been with a three-times-daily or more frequent divided dosing regimen).

Even the TAS-102 team initially doubted that a twice-daily divided dosing regimen would work and was ultimately surprised that the regimen achieved better continuity of administration and efficacy than three-times-daily dosing and resulted in fewer side effects than expected. Tr., 268:19-269:4 (Mr. Mita testified that his colleagues "thought that based on the research papers and their experience up to that point in time, that three times daily or four times daily or even more frequently daily would be more effective; and therefore, they did not believe that there's any possibility for twice daily being effective."); JTX-0012.0860, ¶3; 0861, ¶5. Mr. Mita himself noted that "[b]ased on the available data it was our expectation that the three

times per day dosing would be better." JTX-0012.0860, ¶3. Nothing in the prior art at the time suggested to Mr. Mita, let alone to a POSA, that a twice-daily divided dosing regimen would produce superior results, and a POSA would not have had a reasonable expectation of success using a twice-daily divided dosing regimen based on the data available at the time.

Yet surprisingly, despite Taiho's expectation that a three-times daily divided dosing regimen would be better, the inventors found ***increased efficacy*** with the twice-daily divided dose—"***the opposite of that predicted by Dr. Emura's tests in mice***." JTX-0012.0861, ¶5. And although Mr. Mita expected "that patients on the twice a day dosing would experience significantly more side effects from the higher amount of TAS-102 administered in each dose," they found ***no significant difference in adverse events*** between the twice-daily and three-times-daily divided dosing regimens. JTX-0012.0861, ¶5. These results were "quite surprising" and unexpected given that the data available in the prior art "suggested that 3 to 4 divided doses would be expected to be better." JTX-0012.0862, ¶6.

Mr. Mita's declaration described the results of two Taiho studies, referred to as the 9804 and 9805 studies. Neither study is prior art. In Taiho's 9805 study, TAS-102 was administered at a three-times-daily divided dose of 70 mg/m^2/day up to 80 mg/m^2/day for five days a week followed by two days rest for two weeks every four weeks. JTX-0012.1310. In Taiho's 9804 study, TAS-102 was administered at a

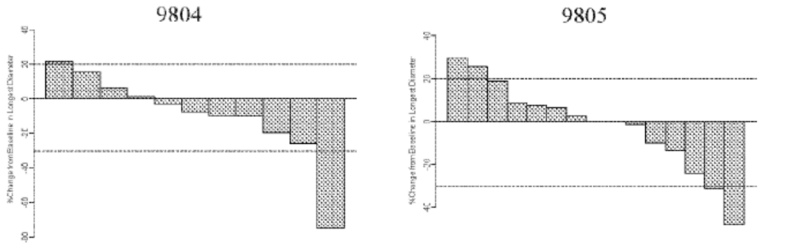
twice-daily divided dose of 50 mg/m^2/day up to 80 mg/m^2/day for five days a week followed by two days rest for two weeks every four weeks. JTX-0012.1309. Mr. Mita's declaration (JTX-0012.0860) and Exhibit Q (JTX-0012.1258) demonstrate that *the 9804 study* (twice-daily divided dosing) *outperformed the 9805 study* (three-times-daily divided dosing) *in all categories related to continuity and efficacy when tested at doses within the claimed range of claim 13*[8]:

	9804	**9805**
Number of days of prolongation of the washout period	2.6 days	4.4 days
Percentage of cases with dose reduction	63%	100%
Relative Dose Intensity	82%	78%
Disease Control Rate (DCR)	75%	67%
Maximum Tumor Reduction (mean, median)	13.1%, 7.4%	0.7%, -2.7%

[8] Exhibit Q shows better efficacy for the 9804 study in both categories, and better continuity in at least 3 of 4 categories, across the doses within the scope of claim 13. In the fourth continuity category, the results were equal or better (i.e., "Number of courses started at the initial dose"). JTX-0012.1258-59. With respect to safety (i.e., adverse events), although Mr. Mita stated that "there was no significant difference between the two studies," he also explained this was unexpected because Taiho's "expectation had been that patients on the twice a day dosing would experience significantly more side effects from the higher amount of TAS-102 administered in each dose" and Exhibit Q reports a number of examples where 9804 outperformed 9805 in terms of side effects as well. JTX-0012.0861, 1258-84.

Given the teachings of Emura-II and Takeda, a POSA would have been surprised to learn that the twice-daily, divided dosing regimen of 9804 demonstrated superior performance over the three-times-daily, divided dosing of 9805.[9] As shown in the waterfall plots below, the 9804 study demonstrated significantly greater tumor reduction:

- Waterfall Plot (9804 study 50, 60 & 80 mg/m^2 vs. 9805 study 60, 70 & 80 mg/m^2)



JTX-0012.1284. The 9804 study also had far better continuity of administration with a mean duration of stable disease of 229 days as compared to 132 days for the 9805 study. Tr., 353:10-354:8 (Goldberg); JTX-0012.1309-10. As compared to the 9805 study, the 9804 study had a shorter washout period, fewer cases of dose reduction, higher relative dose intensity, better DCR, and greater tumor reduction. The evidence demonstrating better continuity is also directly tied to the one of the most important benefits of LONSURF relative to other competitive drugs, namely,

[9] The results were also surprising in view of Emura's later-conducted (non-prior art) mouse studies, which suggested that "2 and 3 times per day dosing were equally effective." JTX-0012.0862 (Mita Decl., ¶ 7).

the fact that it results in both extension of life and better quality of life over that extended time period. Tr., 314:1-16 (Whitten).

Additionally, the 9804 study surprisingly had a comparable, if not better, side effect profile. The 9804 study had fewer incidences of adverse events and adverse drug reactions in many categories, including hematologic toxicity and gastrointestinal toxicity. JTX-0012.1263-80. These results were surprising because Taiho expected "that patients on the twice a day dosing would experience significantly more side effects from the higher amount of TAS-102 administered in each dose." JTX-0012.0861.

These unexpected results amount to a difference in kind, not merely in degree. The 9804 study outperformed the 9805 study in ***at least five different categories related to continuity and efficacy***. Indeed, the mean duration of stable disease for the 9804 study was nearly double that of the 9805 study. Tr., 353:10-354:8, 452:6-15 (Goldberg); JTX-0012.1309-10.

This evidence went unrebutted at trial. Dr. Ratain did not have any criticism of the continuity and safety data presented in Exhibit Q, and rather than question Mr. Mita at trial, Defendants relied on information later submitted to FDA in an attempt to challenge the unexpected results.

Defendants repeatedly argue there is no evidence of unexpected results because the 9804 and 9805 studies did not demonstrate efficacy (D.I. 122 at 10, 38-

40), but this argument is irrelevant in view of Defendant's position that claim 13 does not require efficacy (D.I. 122 at 12). Their argument is also factually incorrect. Mr. Mita presented testimony regarding the unexpectedly better efficacy results for the 9804 study in Exhibit Q. Tr., 275:20-277:1. Further, one goal of the 9804 and 9805 studies was to "document any antitumor activity" by applying the RECIST criteria, and Dr. Goldberg explained that patients in both studies reported stable disease. Tr., 353:10-354:8, 356:4-19, 452:6-14 (Goldberg); JTX-0012.0903, 0906 ("Efficacy was also based on . . . duration of stable disease."). Additional record evidence supports the understanding that stable disease is evidence of efficacy.[10]

Finally, that the 9804 study included breast cancer patients does not prevent comparison of the two studies.[11] Breast cancer tumors and colorectal cancer tumors are both solid tumors, which means they arise from gland-forming organs and tend

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[10] FDA recognized the importance of achieving stable disease in late stage colorectal cancer patients undergoing third line treatment. FDA approved LONSURF based on RECOURSE, which showed a DCR of 44% under a secondary endpoint, with only 1.4% of patients demonstrating a partial response with the remaining demonstrating stable disease. JTX-0023.0006.

[11] Likewise, Dr. Ratain's testimony that "the notion that even Taiho thought [the 9804 results] were great is pretty farfetched" because there were no further studies in breast cancer patients is a red herring. The TAS-102 project was designed to investigate a treatment for colorectal cancer. PTX-534; PTX-533; PTX-1699.0005; PTX-1707.0005 (all prior studies were primarily in gastrointestinal or colorectal cancers). Mr. Mita also explained the only reason why the 9804 study was conducted with breast cancer patients was because of budget and timing. Tr., 269:5-14.

to be responsive to fluoropyrimidines. Tr., 278:22-279:4 (Mita); Tr., 376:8-14 (Goldberg). FTD was also known to be effective against both cancers. Tr., 278:22-279:4 (Mita); Tr., 376:8-377:2 (Goldberg). The RECIST evaluation criteria are used for both cancers. Tr., 278:22-279:4 (Mita). Defendants did not rebut any of this testimony at trial. It is also standard practice to look to similar tumors when evaluating a drug. Tr., 357:11-359:10 (Goldberg). Indeed, Dr. Ratain authored numerous studies that compared different cancer types, using waterfall plots to show the results. Tr., 211:11-25, 214:3-6, 215:6-9 (Ratain).

Having read and understood Mr. Mita's declaration, the supporting evidence, and the prior art of record, the USPTO appreciated the significance of the surprising and unexpected results encompassed by claim 13. In the Notice of Allowance of the '284 patent, the PTO observed that "[t]his claimed twice-daily dosing protocol shows efficacy in human clinical trials, but also shows reduced adverse patient events;" and "[i]t was unexpectedly found that more tumors shrunk when treated with the twice-daily dosing schedule than with the three-dose daily dosing schedule." JTX-0012.1333. That type of "technical finding[]" means that "the court should be extremely reluctant to substitute its opinion for the expertise of the patent office." *MiMedx Grp., Inc. v. Tissue Transplant Tech., Ltd.*, 354 F. Supp. 3d 742, 753 (W.D. Tex. 2018) (quoting *Ingersoll-Rand Co. v. Brunner & Lay, Inc.*, 474 F.2d 491, 496 (5th Cir. 1973)). "Where the PTO has made a finding, the attacker of a

patent's validity has 'the added burden of overcoming the deference that is due to a qualified government agency.'" *Id.* (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984), *overruled on other grounds in Therasense, Inc. v. Becton, Dickinson and Co.*, 649 F.3d 1276 (Fed. Cir. 2011)). Defendants have not carried either burden here.

2. The Real-World Performance of LONSURF® Provides Additional Objective Evidence of Non-Obviousness

For objective indicia evidence to support non-obviousness, the evidence must be "attributable to the inventive characteristics of the discovery as claimed in the patent." *Apple Inc. v. Samsung Elec. Co.*, 839 F.3d 1034, 1068 (Fed. Cir. 2016) (*en banc*). There is a "presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product is the invention disclosed and claimed in the patent." *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1067 (Fed. Cir. 2020). The real world performance of LONSURF® has a presumptive nexus to claim 13 and provides additional objective evidence of non-obviousness based on satisfaction of a long-felt but unmet need, industry praise, and commercial success.

Importantly, the nexus between LONSURF® and claim 13 is not defeated by the fact that some of the limitations are present in the prior art. "[T]he separate disclosure of individual limitations, where the invention is a unique combination of [multiple] interdependent properties, does not negate a nexus. Concluding otherwise

would mean that nexus could never exist where the claimed invention is a unique combination of known elements from the prior art." *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1378 (Fed. Cir. 2021). As is common in disease treatment regimens, the dosing regimen disclosed in claim 13 works as an interdependent whole, because each claimed component (the division, the dosage, the schedule) takes on different significance when incorporated into the overall system. Put simply, "dose *some other drug* for 5 days on" is different than "dose *LONSURF*® for 5 days on." Defendants' improper dissection of claim 13's components fails to consider whether there is a nexus to "the claimed invention *as a whole*," and contravenes the Federal Circuit's instruction in *Chemours.*

i. The Benefits of LONSURF® Are Tied to Claim 13 of the '284 Patent

a. The Presumption of Nexus Applies

Here, Taiho presented undisputed evidence that LONSURF®'s recommended dosage regimen, as described in the product label, is embodied by claim 13. JTX-0151. The label is the guideline that physicians use to prescribe LONSURF® (Tr., 359:18-360:12 (Goldberg)) and incorporates the dosing scheduled applied in the RECOURSE study upon which FDA approval was granted (Tr., 320:20-23 (Whitten)). Defendants do not seriously challenge these points. Instead, Defendants assert that LONSURF® is not commensurate in scope with claim 13, arguing: (1) there is no evidence "suggesting that 100% of the prescriptions written for

LONSURF® were tied to the dosage range of claim 13"[12]; (2) claim 13 is broader than the label for LONSURF®, and (3) other patents cover LONSURF®. Each of these arguments fails.

1. The Evidence Shows that LONSURF® Is Dosed in Accordance with Its Label

Contrary to Defendants' brief, Taiho presented unrebutted evidence that LONSURF® is dosed in accordance with its label. Timothy Whitten, the president and CEO of Taiho Oncology, Inc., testified that in Phase III studies for LONSURF®, patients received the FDA-approved dosing regimen. Tr., 320:20-23 (Whitten). He also explained it is "important that [patients] get the proper dose and the proper schedule of Lonsurf if they wanted to achieve the optimal benefit from the drug." Tr., 320:2-4; *see also* PTX-1738.0006 (clinicians should "avoid unnecessary dose reductions"). Further, Dr. Goldberg testified that the most common dosage that he prescribed was "35 milligrams per meter squared twice daily . . . [f]or a total of 70 milligrams per meter squared per day." Tr., 360:7-12.

Moreover, Defendants misinterpret the label when arguing that the dosing range in the LONSURF® label is broader than claim 13. D.I. 122 at 37. LONSURF®'s label states that "[t]he recommended dosage of LONSURF is 35

[12] Defendants, however, presented no evidence at trial that there are any known off-label uses for LONSURF®, and Mr. Hofmann was unable to identify any such uses when questioned by the Court. Tr., 520:21-521:4.

mg/m^2 up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily." JTX-0151.0002. The first number is mass per m^2 or BSA, while the second number is only mass. In other words, the "80 mg per dose" is the actual amount of drug administered based on BSA. As shown in Section 2.1 of the label (Table 1), so long as a person's BSA is below 2.3, the "recommended dosage" remains 35 mg/m^2 twice daily or 70 mg/m^2/day in 2 divided portions.

Table 1 Recommended Dosage According to Body Surface Area (BSA)

BSA (m2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15mg	20mg
< 1.07	70	35	1	1
1.07 - 1.22	80	40	0	2
1.23 - 1.37	90	45	3	0
1.38 - 1.52	100	50	2	1
1.53 - 1.68	110	55	1	2
1.69 - 1.83	120	60	0	3
1.84 - 1.98	130	65	3	1
1.99 - 2.14	140	70	2	2
2.15 - 2.29	150	75	1	3
≥2.30	160	80	0	4

JTX-0151.0003; Tr., 334:7-13 (Whitten). For the dosage amount in terms of BSA to fall outside the claimed 50-70 mg/m^2/day range, a person's BSA must either be below 1.07 or exceed 2.3. Thus, contrary to Defendants' assertion, the recommended dosage amount in the LONSURF® label is not outside the claimed range.

2. The Five Days, Two Days Off Schedule Is Necessary to Practice Claim 13

Defendants also argue that "the Lonsurf® label requires a 16-day rest period after two weeks of dosing on the weekends off schedule" while "claim 13 does not recite anything about a 28-day schedule with a 16-day rest period." D.I. 122 at 37. However, Defendants do not identify a single instance where claim 13 is being

practiced other than in accordance with the dosing regimen set forth in the LONSURF® label. Defendants' characterization of the label is misleading as well. The label does not refer to a "16-day rest period." Rather, it states that LONSURF® should be administered on "Days 1 through 5 and Days 8 through 12 of each 28-day cycle." JTX-0151.0001. Thus, the label clearly requires that LONSURF® be administered for 5 days with a 2 day rest period during each week when treatment is given. These instructions are commensurate in scope with claim 13, which requires administration "for 5 days followed by 2 days off treatment in the week on a one-week dosing schedule," i.e., during the weeks when treatment is given. JTX-0001.0009, 9:20-34. To administer LONSURF® 5 days on, 2 days off for two weeks out of a 28 day cycle according to the label, it is necessary to practice the 5 days on, 2 days off recited in claim 13.

3. The Existence of Other Patents Does Not Discount the Objective Evidence

Defendants argue that the existence of other patents covering LONSURF® precludes a presumption of nexus "because one or more of the asserted patents cover at least some aspect of the Lonsurf® product." D.I. 122 at 44. Defendants rely on *Fox Factory, Inc. v. SRAM, LLC*, for the proposition that to be entitled to the presumption of nexus the patentee must "demonstrate that the product is essentially the claimed invention." 944 F.3d 1366, 1374 (Fed. Cir. 2019). However, as Dr. Rao testified, merely because other patents cover LONSURF® does not mean that claim

13 is not necessary for the commercial success of LONSURF®. Tr., 489:24-491:8. Rather, there may be multiple patents that cover a product, each of which contributes to commercial success. *Id.* Further, as *Fox* acknowledges, the patentee can still prove nexus by providing the evidence is "attributable to the claimed" invention, which Taiho shows below. *Fox*, 944 F.3d at 1378.

"A patent has been called a 'blocking patent' where practice of a later invention would infringe the earlier ['blocking'] patent." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018). But Defendants presented no competent analysis at trial as to whether the practice of the '500 patent's claims would infringe the earlier patents—that is, whether the patent is a "blocking patent" at all. Indeed, the '500 patent was reissued and delisted from the Orange Book. Tr., 474:15-19 (Rao), Tr., 513:9-23 (Hofmann). Further, the '475 patent expired in 2016—shortly after the launch of LONSURF®.

Moreover, a statutory safe harbor exists allowing others to research and develop new technologies to be ready for launch as soon as a patent expires. *See* 35 U.S.C. § 271(e)(1); *see also Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 571 F. Supp. 3d 281, 324-25 (D.N.J. 2021) (noting that the safe harbor provision weighed against finding that other patents deterred innovation).

b. The Evidence Shows that Claim 13 Led to the Benefits of LONSURF®

LONSURF® was approved based on a specific dosing schedule, dosing frequency, and dose, as tested in the RECOURSE trial. The same dosing schedule, dosing frequency and dose is reflected in the LONSURF® label and is covered by claim 13. Tr., 374:7-17 (Goldberg). In turn, the claimed dosing schedule, dosing frequency and dose of claim 13 is responsible for the recognized benefits of LONSURF®, including the benefits realized by patients (e.g., extending overall survival, quality of life and more tolerable side effects), particularly as compared to its competitors—most notably, Stivarga®. Tr., 323:19-324:1 (Whitten); Tr., 364:1-365:14, 374:7-17 (Goldberg); Tr., 464:6-12 (Rao); JTX-0131.0010-11; JTX-0139.0054. More specifically, those benefits are directly attributable to the manner in which LONSURF® was approved for administration by FDA, including the approved dosage and dosing regimen as reflected in the product label, which is directly covered by the claimed invention.

ii. LONSURF® Satisfied a Long-Felt, But Unmet Need for a Stage IV Colorectal Cancer Therapy that Extends Life While Maintaining Quality of Life

To make a *prima facie* showing of long-felt but unsolved need, the patentee "must establish that (1) a POSA recognized a problem that existed for a long period of time without a solution, (2) the long-felt need had not been satisfied by another before the claimed invention, and (3) the invention in fact satisfied the long-felt

need." *Immunex Corp. v. Sandoz Inc.*, 395 F. Supp. 3d 366, 405 (D.N.J. 2019) *aff'd*, 964 F.3d 1049 (Fed. Cir. 2020).

LONSURF® satisfied a long-felt unmet need in the treatment of advanced colorectal cancer, including the need for better treatment options that would allow patients to live longer and maintain quality of life.[13] Tr., 355:18-22 (Goldberg), 312:7-314:16 (Whitten). This need existed before the filing of the '284 patent in January 2005.[14] Tr., 360:13-24, 448:12-449:8 (Goldberg). Prior to LONSURF®, there was only one other drug approved to treat patients with Stage IV colorectal cancer that have undergone first and second lines of therapy, Stivarga®. Tr., 361:18-21 (Goldberg); Tr., 461:3-10 (Rao). Other approved therapies that may be used in third-line treatment, such as injectable drugs, are approved for different indications and to treat different, specific subsets of patients. Tr., 322:1-17 (Whitten). The fact that Lonsurf satisfied this need was recognized throughout the industry as well. Tr.,

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[13] The fact that LONSURF® was approved later is irrelevant. "[P]atentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest." *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms., Inc., USA*, 748 F.3d 1354, 1360 (Fed. Cir. 2014).

[14] That Mr. Whitten was unable to testify about the state of the art in 2005 is irrelevant. Mr. Whitten was not at Taiho at this time (Tr., 309:12-16 (Whitten)), and Defendants' technical expert, Dr. Goldberg, provided testimony about this need (Tr., 360:13-24, 448:12-449:8 (Goldberg)).

365:15 – 366:22 (Goldberg); PTX-0530.0001, 5; PTX-0474.0001; PTX-0483.0001; PTX-0485.0001-2; PTX-0476.0001; PTX-0475.0014.

Through the dosing regimen of claim 13, LONSURF® provided a better option for such patients than what was previously approved and available. More specifically, LONSURF® was more tolerable—a primary consideration for late-stage cancer drugs—than Stivarga®. Tr., 323:19-324:1 (Whitten); 364:1-365:14 (Goldberg); Tr., 463:3-464:2 (Rao); JTX-0131.0010-11; JTX-0139.0054. Thus, LONSURF® qualified for the FDA's fast-track approval, which expedites the review of drugs to treat serious conditions and fill an unmet medical need. Tr., 315:1-23 (Whitten); PTX-0522.0001; PTX-1251.0001.

Defendants' argument that LONSURF® does not provide any benefit over palliative care or investigational drugs is contradicted in the record. The RECOURSE study demonstrated a 1.8 month median extension in life, i.e., a "clinically relevant prolongation of overall survival." Tr., 317:5-19, 319:6-18 (Whitten); JTX-0023.0006, 09.[15] Patients on LONSURF® also showed improved

[15] Although Dr. Ratain takes issue with the findings in the New England Journal of Medicine that report that Lonsurf was associated with a "significant improvement in overall survival," arguing that this relates to statistical significance and not clinical significance, the authors also report that "TAS-102 was associated with a **clinically relevant prolongation of overall survival** in essentially all treatment subgroups." JTX.0023.0009 (emphasis added).

quality of life as indicated by the hazard ratio and ECOG data, which measure risk of death and ability to function, respectively. Tr., 319:6-18 (Whitten); JTX-0023.0005-08. Additionally, the number of patients that enter clinical trials is quite low (particularly when compared to the high number of patients that have been treated with LONSURF®), demonstrating that it is not a realistic option for most patients. Tr., 314:17-24, 327:18-328:1 (Whitten).

iii. The Claimed Dosing Regimen Led to Industry Praise for LONSURF®

Evidence of industry praise of a claimed invention "weighs in favor of [] nonobviousness" because "[i]ndustry participants, especially competitors, are not likely to praise an obvious advance over the known art." *Apple*, 839 F.3d at 1053.

Here, the RECOURSE results that led to FDA's approval of LONSURF® were published by the prestigious NEJM. Additionally, patient advocacy groups, which are neutral groups that support patients, have discussed LONSURF® favorably. Tr., 372:5-373:11 (Goldberg); Tr., 312:6-314:16 (Whitten); *see, e.g., Janssen*, 571 F.Supp.3d at 317-19 (relying on trade publication articles and expert testimony in finding that industry praise weighed in favor of non-obviousness in ANDA case). LONSURF® also has emerged as a preferred treatment option for medical oncologists, due to its efficacy and tolerability. Tr., 323:19-324:1 (Whitten); Tr., 364:1-365:14, 374:7-17 (Goldberg); Tr., 464:6-12 (Rao); JTX-0131.0010-11; JTX-0139.0054.

iv. LONSURF® Has Been Commercially Successful

Commercial success provides strong evidence of non-obviousness where, as here, there is a nexus between the success and the claimed invention. *See Alcon Research Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1371 (Fed. Cir. 2012); *see also Pharmacyclics,* 556 F. Supp. 3d at 400. The patented invention does not need to be "solely responsible for the commercial success in order for this factor to be given weight." *Cont'l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991).

LONSURF® has been a marketplace success. Net sales since launch have exceeded $1.6 billion. Tr., 324:25-325:11 (Whitten); Tr., 458:1-10 (Rao); PTX-1718.0002; PTX-1725.0002. Taiho achieved this commercial success despite having no commercial presence in the United States before LONSURF® and, thus, no brand reputation. Tr., 327:1-17 (Whitten). By contrast, LONSURF's main competitor is Stivarga®, marketed by Bayer, a household pharmaceutical name with an established reputation. Tr., 327:1-17 (Whitten); Tr., 459:23-462:10 (Rao). Shortly after its launch, LONSURF® began to outperform its closest competitors, Stivarga® and Xeloda®—both of which had been on the market for far longer. Tr., 468:2-9 (Rao); Tr., 323:15-324:1 (Whitten); PTX-1722.0001; PTX-1727.0004. Finally, LONSURF®'s sales have continued to rise even though Taiho has significantly decreased the amount it spends on promotion of LONSURF®. Tr.,

326:6-25 (Whitten); *see Bial-Portela & CA. S.A. v. Alkem Labs. Ltd.*, No. CV 18-304-CFCCJB, 2022 WL 4244989, at *14-15 (D. Del. Sept. 15, 2022) (finding that the fact that "revenue and profits rose . . . despite a drop in marketing spend" supported commercial success).

Defendants argue that the complexity of the LONSURF® dosing schedule was a barrier to its commercial success. *See* D.I. 122 at 45. But the evidence shows that the benefits of the claimed dosing regimen, including efficacy and tolerability, are important drivers of LONSURF®'s commercial success. Tr., 323:19-324:1 (Whitten); Tr., 364:1-365:14, 374:7-17 (Goldberg); Tr., 464:6-12 (Rao); JTX-0131.0010-11; JTX-0139.0054. These patented benefits are emphasized in Taiho's marketing materials for LONSURF® because they are seen as key differentiators for LONSURF®. Tr., 469:19-470:13 (Rao); JTX-0040.0008; JTX-0133.0002. While JTX-0138.0001, 0013 and JTX-0140.0014 may have identified LONSURF's® dosing schedule as "complicated," neither reported an actual negative impact on sales. Indeed, LONSURF® sales quickly overtook Stivarga sales (Tr., 468:2-9 (Rao); Tr., 322:21-324:1 (Whitten); PTX-1722.0001; PTX-1727.0004) despite the perception that the Stivarga schedule was "easier." Further, market research determined that 70% of oncologists preferred LONSURF® over Stivarga because of its superior tolerability profile (Tr., 323:19-324:1 (Whitten); JTX-0131.0010), a feature made possible as a result of the FDA-approved dosing

schedule based on the Phase III RECOURSE study (Tr., 323:19-324:1 (Whitten); Tr., 364:1-365:14, 374:7-17 (Goldberg); Tr., 464:6-12 (Rao)).

The facts here are distinguishable from *Merck & Co. v. Teva Pharms. USA, Inc.,* 395 F.3d 1364, 1376-77 (Fed. Cir. 2005). In *Merck*, the patent claimed weekly dosages of alendronate monosodium trihydrate—a compound sold under the brand name Fosamax. Prior to seeking FDA approval for the weekly dosage version of Fosamax, Merck had already received an "exclusive statutory right, in conjunction with FDA marketing approvals, to offer Fosamax at any dosage for the next five years." *Id.* at 1377. The court then relied on this exclusivity in finding that Merck's evidence of commercial success was "weak." *Id.*

By contrast, when the dosing regimen of claim 13 was developed, LONSURF® had yet to be approved by FDA and no such exclusivity existed. As discussed above, prior to the launch of LONSURF®, Stivarga® and to a lesser extent Xeloda® were already being used to treat Stage IV colorectal cancer, and despite this competition, LONSURF® was able to achieve success. Tr., 323:7-12 (Whitten).

Finally, the Federal Circuit has found that commercial success can indicate non-obviousness in ANDA cases. In *Alcon*, the fact that the drug was "'an outstanding commercial success,' achieving nearly 70% market share within two years of its launch, accounting for nearly $2 billion in sales within ten years, and garnering wide-spread praise within the industry" supported the district court's

holding that the claims were not obvious. 687 F.3d at 1371; *see also Leo Pharm.*, 726 F.3d at 1358; *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 723 F.3d 1363, 1372-73 (Fed. Cir. 2013), *rev'd on other grounds*, 574 U.S. 318 (2015) (commercial success of FDA-approved drug supported non-obviousness).

IV. DEFENDANTS FAILED TO PROVE BY CLEAR AND CONVINCING EVIDENCE THAT CLAIM 13 OF THE '284 PATENT IS NOT ADEQUATELY DESCRIBED

Written description is assessed from the perspective of a POSA and the fundamental factual inquiry is whether the specification conveys with reasonable clarity ***to a POSA*** that, as of the filing date, the applicant was in possession of the claimed invention. 35 U.S.C. § 112; *Takeda Pharm. Co. v. Zydus Pharms. USA, Inc.*, 743 F.3d 1359, 1368 (Fed. Cir. 2014); *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Defendants failed to follow this fundamental inquiry and to provide any clear and convincing evidence that the specification does not reasonably convey to a POSA that the inventors were in possession of the invention of claim 13.

First, Defendants argue that Dr. Ratain "concluded there is no description in the specification of the actual administration of FTD and tipiracil in two divided doses on the weekends off schedule to patients with digestive cancer or colorectal cancer specifically." D.I. 122 at 50. The issue is not whether there is an explicit description of the "actual administration," but rather, whether in a POSA's view, the

specification adequately describes the subject matter of claim 13. Dr. Ratain's testimony does not address the perspective of a POSA. Tr., 102:6-8; 124:3-12; 204:3-5. And the written description requirement does not demand either examples or an actual reduction to practice. *E.g.*, *Streck, Inc. v. Research & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1285-1286 (Fed. Cir. 2012).

Second, Defendants argue that the specification "does not describe or discuss administering TAS-102 in two divided doses per day to human patients with *digestive* cancer generally, much less specifically with *colorectal* cancer" and that Example 4 relates to *breast* cancer rather than *colorectal* cancer. D.I. 122 at 48 (emphasis added). This argument, however, ignores other portions of the specification and Dr. Goldberg and Mr. Mita's trial testimony about a POSA's knowledge and understanding of the specification and what it discloses.

Dr. Goldberg, who is qualified as a POSA (Tr., 339:18-342:4), and/or Mr. Mita, a co-inventor of the '284 patent, testified that: (i) the results of the 9804 and 9805 studies can be compared even though the cancers involved were different (Tr., 357:11-359:10, 379:2-5 (Goldberg)[16]; Tr., 274:6-11 (Mita)); (ii) breast and digestive

[16] The fact that Taiho did "further Phase I studies" (Tr., 358:9-13) does not demonstrate that the inventors were not in possession of the claimed invention. Actual reduction to practice is not required. And, Dr. Goldberg explained this was

cancers are solid tumors, commonly spread to liver and lung, and commonly respond to cytotoxic agents, and there is a lot of data to show that oral fluoropyrimidines[17] are active in both breast and colorectal cancer, FTD is effective against both breast cancer and colorectal cancer, and the same evaluation criteria for solid tumors (RECIST criteria) were used (Tr., 376:8-378:6 (Goldberg); Tr., 278:22-279:4 (Mita)); and (iii) Example 4 is relevant to showing "possession" of twice-daily divided dosing for colorectal cancer (Tr., 376:2-378:6 (Goldberg)), including because cross-study comparisons are done all the time in oncology (Tr., 354:9-16 (Goldberg)). Defendants decided not to cross-examine Mr. Mita, so his testimony is completely unrebutted.

Third, Defendants and Dr. Ratain failed to recognize that each limitation of claim 13 is expressly described in the specification. The specification describes the use of the TAS-102 in humans for treatment of specific cancers, including colorectal cancer, and the daily dosage amounts and dosing schedule, including the twice-daily divided dosing as claimed in the '284 patent. JTX-0001.0005-09, 2:61-67, 4:52-56, 5:32-5, 7:51-9:2 (Examples 3 and 4). It not only recites a narrow range of possible

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likely done to confirm safety and dose tolerability given that because breast cancer patients tend to be more heavily pretreated than GI cancer patients. Tr., 358:9-22.

[17] A fluoropyrimidine is a type of antimetabolite, including FTD.

total daily doses and a narrow number of daily divided doses, but it also expressly recites a particular preference for 50-70 mg/m^2/day (JTX-0001.0006. 4:54-56) and 2-3 daily divided doses (JTX-0001.0007, 5:32-35). *See also* Tr., 375:19-22 (Goldberg). The preferred range of daily divided doses directly corresponds to twice-daily divided dosing as claimed in claim 13. Contrary to Defendants' argument, the specification repeatedly describes twice-daily divided dosing. JTX-0001.0001, 05-08, Abstract, Fig. 3, 2:49-52, 2:55-56, 2:66-67, 3:5-6, 3:33-36, 3:64-67, 4:52-53, 5:30-31, 5:33-35, 5:56-59, 8:43-9:2 (Example 4); JSUF, ¶40. It also describes aspects of TAS-102, the dosage amount, calculations for body surface area, dosage interval of 6 hours or more, and the different conditions that can be treated. JTX-0001.0006-07, 3:46-5:60. Thus, each element of claim 13 is expressly described. *See Tas v. Beachy,* 626 F. App'x 999, 1004-1005 (Fed. Cir. 2015). Further, although not required, the '284 patent specification includes specific, clinical examples of the use of TAS-102 in both digestive cancer and breast cancer patients. JSUF, ¶¶41-42; JTX-0001.0008-09, 7:54-59, 8:45-49, 8:56-9:2; Tr., 263:6-10 (Mita).

For the foregoing reasons, Defendants failed to prove by clear and convincing evidence that in a POSA's view the inventors were not in possession of the subject matter of claim 13.

V. CONCLUSION

For the above reasons, Defendants have failed to meet their burden of proving by clear and convincing evidence that claim 13 of the '284 patent is invalid for obviousness or lack of written description.

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

The foregoing document complies with the type-volume limitations of the Court's Standing Order Regarding Briefing in all Cases dated November 10, 2022 and the Stipulation and [Proposed] Order Regarding Post-Trial Briefing Schedule (D.I. 158 in C.A. No. 19-2368). The text of the foregoing brief, including footnotes, was prepared in Times New Roman 14 point. According to Microsoft Word, the text of the foregoing brief, including footnotes, contains 12,297 words.

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